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Failure is not an Alternative: A Systematic Review of the Prognostic Factors of Cardiorenal Syndrome

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Abstract

Cardiorenal syndrome (CRS) is a pathophysiological condition of the heart and kidneys. Cardiac and renal illnesses are prevalent and commonly overlap to substantial increase mortality, morbidity, and cost. Smoking, hypertension, coronary artery disease, diabetes, sepsis, and labs of blood urea, serum creatinine, eGFR, and LVEF were identified as death risk factors. Up to 40% of decompensated HF patients exhibit with CRS 1. Just 9% of patients with acute HF had normal renal function. Those with type 4 CRS have a 49% higher mortality risk.

Increasing AKI severity was related with worse outcomes, including a higher fatality rate and longer stay in the critical care unit. Anemia predicted rehospitalization in individuals with renal failure. Reduced basic eGFR, lower serum albumin, and the use of diuretics were risk factors for the development of CRS1 in senior AHF patients. Spironolactone was emonstrated to be a safe and effective therapy option for patients with acute heart failure at risk for CRS.

Diabetes and hypertension were found as the two most important risk factors in patients with CRS. Acute renal functional impairments were particularly connected to obesity (increased leptin levels and anthropometric variables) and high blood pressure. The extent to which this hyperfiltration results in glomerular and tubulointerstitial fibrosis and progressive renal disease may rely on various factors including systemic and renal inflammation. Insulin-induced hyperinsulinemia can reduce the quantity of uric acid excreted by the kidneys due to its ability to stimulate urate-anion exchanger and/or sodium-dependent anion co-transporter in the renal proximal tubule. Increased circulating norepinephrine is associated with increased vasoconstriction (or lower compliance) and impaired heart rate response in elderly individuals with CHF.

Cardiorenal syndrome Type 1 is typically associated with Acute Decompensated Heart Failure. This is caused by a diuresis-induced stimulation of the RAAS, which results in sodium retention and precipitates CRS via renovascular processes. Numerous resistance mechanisms to diuretics have been examined. Cardiopulmonary bypass and renal ischemia-reperfusion injury initiate a sequence of events that leads in cellular damage and organ failure. Both the kidney and the heart release Tumor Necrosis Factor (TNF), a potent proinflammatory cytokine. Anti-TNF medication can minimize these consequences.

Studies have shown that NT-pro BNP maintains a favorable prognosis for individuals with heart failure and renal impairment. Increased troponins in CKD patients are indicative of continued myocardial injury, left ventricular dilatation, and reduced left ventricle systolic and diastolic function.

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Introduction

Cardiorenal syndrome (CRS) is a pathophysiological condition of the heart and kidneys in which acute or chronic malfunction in one organ can cause acute or chronic dysfunction in the other. Cardiac and renal diseases are prevalent and commonly overlap to substantial increase mortality, morbidity, and the complexity and expense of care [1, 2]. In 2004, the National Heart, Lung, and Blood Institute Working Group evaluated the interaction between

the heart and kidney and defined CRS as the result of interactions between the kidneys and other circulatory compartments that increase circulating volume, which worsens the symptoms of heart failure (HF) and disease progression. A recent classification of CRS proposed by the 7th Acute Dialysis Quality Initiates consensus conference has divided the syndromes into those that are "Cardiorenal" in which cardiac dysfunction leads to kidney dysfunction and those that are "Renocardiac" in which primary kidney dysfunction leads to cardiac dysfunction [3].

The individual prognosis and economic consequences of CKD or cardiac disease, especially congestive heart failure (CHF), are well known. According to the Global Burden of Disease survey, the global prevalence of CKD in 2015 was predicted to be around 323 million [4]. In addition to the association between CHF and frequent hospitalizations, cardiovascular disease (CVD) is the leading cause of death among the CKD population [5, 6].

Considering the aging population, longer exposure to prevalent risk factors such as uncontrolled hypertension, obesity, diabetes, and vascular illnesses, as well as breakthroughs in medical therapy, the prevalence of CKD and HF is predicted to increase [7]. Patients with decreased renal function also had a longer hospital stay, greater hospital expenses, a higher hospital mortality rate, and an increased likelihood of readmission.

Consequently, it is essential to comprehend the many risk factors contributing to the spread of this illness. This systematic study aimed to examine the prognostic aspects of cardiorenal syndrome and throw light on potential future directions.

Results

Using the terms "Cardiorenal syndrome," "Prognosis," and "Prognostic factors," a comprehensive search of the medical literature was conducted. A total of 583 results were discovered across multiple databases. After a review of the article's title and abstract, 59 articles were selected. To refine the search, further inclusion and exclusion criteria were implemented. The quality of the remaining submissions was evaluated, and 21 papers were ultimately considered for this Review paper.

Included in the inclusion criteria were original studies, observational studies, and clinical trials. Exclusion Included in the criteria were narrative reviews, editorials, brief communications, Case reports, case series, review articles, articles not written in English, and articles for which the complete text was unavailable.

Eight of the twenty-one studies included in the study to evaluate the prognostic result of CRS patients evaluated the role of various treatment approaches, while the remaining thirteen evaluated the involvement of patient risk factors and disease biomarkers. There were eleven observational studies, eight randomized controlled trials, one meta-analysis, and one case report.

Hypertension and diabetes were much more prevalent among patients with Cardiorenal syndrome (CRS) compared to those without CRS, according to research [8]. More than 60 years of age, smoking, hypertension, coronary artery disease, diabetes, sepsis, and labs of blood urea, serum creatinine, eGFR, and LVEF were identified as death risk factors [9]. In a number of studies, increasing AKI severity was related with worse outcomes, including a higher fatality rate, a longer length of stay in the critical care unit, and a longer LOS in hospital.

Several biomarkers were employed to evaluate renal function, including urinary angiotensinogen (uAGT), urinary neutrophil gelatinase-associated lipocalin (uNGAL), plasma neutrophil gelatinase-associated lipocalin, urinary IL-18 (uIL-18), urinary kidney injury molecule-1, and urinary albumin-to-creatinine ratio. The greatest predictor of both primary and secondary outcomes was uAGT [10]. Lower hemoglobin levels and Creatinine clearance were similarly predictive of outcomes and were associated with an increase in rehospitalizations. Found that anemia predicted rehospitalization in individuals with renal failure. In addition to renal biomarkers, heart function biomarkers are significant in determining outcomes. Kremneva et al. concluded that post-CABG ACS patients with greater troponins were more likely to develop AKI. A worse prognosis was predicted by a GFR less than 60 and a pro BNP greater than 4,467. Reduced basic eGFR, lower serum albumin, and the use of diuretics were risk factors for the development of CRS1 in senior AHF patients The levels of the inflammatory markers LPS, TNF-, IL-6, IL-18, and MPO are significantly greater in the CRS type 1 and AHF groups than in the Control group.

Table 1 displays the numerous Cardiorenal Syndrome prognostic variables described in the many studies included in the literature study.

Table 1: Prognostic Factors for Cardiorenal Syndrome

Patient risk factors	Biomarkers	Treatment
1. **HYPERTENSION** Salim et at 2017 Prothasis et al, 2020	1. TROPONIN Kremneva et al, 2018	1. DIURETICS Verbrugge et al 2018 Iniguez et al, 2022
2. **DIABETES** Salim et at 2017 Prothasis et al, 2020	2. **ProBNP** Wilfried Mullens Et al, 2008	3. **ANTI INFLAMMATORY - ANAKINRA, ANTI-TNF** Buckley et al, 2022
3. **SMOKING** Prothasis et al, 2020	4. **Urinary angiotensinogen (uAGT)** Chunbo Chen at al 2016	3. **PERITONEAL DIALYSIS** Shao et al, 2018
3. **PERITONEAL DIALYSIS** Shao et al, 2018	5. **Urinary neutrophil gelatinase-associated lipocalin (uNGAL)** Chunbo Chen at al 2016	4. **REDUCTION IN INTRA ABDOMINAL PRESSURE** Wilfried Mullens Et al, 2008
5. **CORONARY ARTERY DISEASE** Prothasis et al, 2020	6. **Plasma neutrophil gelatinase-associated lipocalin** Chunbo Chen at al 2016	5. **NICORANDIL** Du et al, 2021
6. **AGE > 60 years** Prothasis et al, 2020	7. **Urinary IL-18 (uIL-18)** Chunbo Chen at al 2016	
7. **AKI SEVERITY** Vandenberghe et al, 2015 Prothasis et al, 2020 Wilfried Mullens Et al, 2008	7. **Urinary kidney injury molecule-1** Chunbo Chen at al 2016	
8. **ANEMIA** Tamhane et al, 2008	8. **Urinary albumin-to-creatinine ratio** Chunbo Chen et al 2016	
9. **LVEF** Prothasis et al, 2020	9. **Inflammatory markers LPS, TNF-α, IL-6, IL-18** Virzi et al, 2019	
	10. **CREATININE** Tamhane et al, 2008 Prothasis et al, 2020	
	11. **SERUM ALBUMIN** Wenxue Hu et al 2016	

Different studies utilized a variety of therapy interventions to determine the most effective means of achieving a better disease outcome. Spironolactone was demonstrated to be a safe and effective therapy option for patients with acute heart failure (AHF) at risk for CRS (Verbrugge et al., 2018). Patients with CRS1 showed a greater incidence of diuretic resistance. Comparing combined diuretic to Stepped Dose Furosemide, the same renal recovery, diuresis, vascular decongestion, and side effects were seen. Nicorandil therapy lowered BNP, S Cr, and Cys-C levels and enhanced LVEF in patients with CRS type Anakinra exhibited considerable anti-inflammatory benefits and lowered CRP by 84%, while placebo had no impact. The role of peritoneal dialysis (PD) in Type 2 CRS was evaluated. The non-Type 2 CRS group showed enhanced survival on PD, however the CRS group did not exhibit increased survival. However, PD remains a realistic and safe palliative treatment option for Type 2 CRS In patients with impaired renal function and elevated intra-abdominal pressures, the reduction of intra-abdominal pressure was another innovative treatment evaluated. It was discovered to significantly improve patient outcomes.

Table 2 provides a detailed summary of the data acquired from numerous investigations on the prognosis of Cardiorenal syndrome.

Table 2: Cardiorenal Syndrome Prognostic Factors Review of the Medical Literature

Author Name, Year	Study design	Study Population, Sample Size	Mean Age n sex of patients	Baseline Cardiac Function	BaselineRenal Function	Prognostic factor Studied	Intervention Studied	Findings	Limitations
(1). Prothasis et al, 2020 (48)	single-centric, cross-sectional study conducted amongst the patients admitted to medicine wards and ICCU	CRS types T1 49 T2 23 T3 3 T4 20 T5 5	56 yrs mean age 60% males	LVEF = 39.63%	eGFR = 21.50 Majority patients 48.42% had RPD Grade 1 39.58% pts of stage 4 CKD	M/C Risk factor = HTN	CRS T 1, 2, 3 = conservative treatment CRS T 4, 5 = Dialysis	45.83% mortality RF a/w mortality: age more than 60yrs, smoking, HTN, CAD, DM, sepsis, and labs of blood urea, serum creatinine, eGFR, and LVEF	-single-centeric study with a small sample size -Cystatin C was not estimated -Detailed history and follow up not done
(2) Salim et at 2017 (47)	monocentric, cross-sectional study	563 Chronic Heart Failure Pts(With and W/O CRS)	Mean age of pts with CRS = 67 yrs, 60% males without CRS = 61 yrs, 53.1% males	LVEF in the CRS pts = 33.50 ± 8.52 NYHA class III and IV was reported in 25.6% in the CRS vs. 13.3% in the group without CRS ($p < 0.0001$	Pts with CRS S. Cr = 0.67 ± 0.36 BUN = 16.84 ± 8.72	The deterioration of renal function in chronic renal failure is associated with poor prognosis,	the % of pts with HTN and DM was significantly higher in the CRS group compared to the group without CRS (55.3% and 42%, respectively, in the CRS group vs. 39.5% and 26.6%, respectively, in the group without CRS, $p < 0.0001$).	Patients with CRS had higher rates of cardiac death and re-hospitalization due to worsening heart failure than those without CRS.	-observational study and reflects the data from patients only from a single center, - Severe patients on hemodialysis werent included -cause-consequence relationship cudnt be established
(3) Iniguez et al, 2022 (54)	pilot double-blind RCT	80 CRS Type 1 patient -40 to the Stepped Dose Furosemide(SF) and 40 to the Combined Diuretic(CD) group	80 CRS Type 1 patient -40 to the Stepped Dose Furosemide(SF) and 40 to the Combined Diuretic(CD) group	BNP = 2631 ± 1713	Urinary volume (ml/ day) = 1266.57	Therapeutics for CRS-1, the use of CD V/S SF.	Pts with CRS1 & a high risk of resistance to diuretics, the use of CD compared to SF offers the same results in renal recovery, diuresis, vascular decongestion and adverse events		-pilot single-center study -without an a priori calculation of sample size
(4) Verbrugge et al 2018 (55)	RCT	80 AHF patients with CRS					open-label oral spironolactone 25 mg OD given upfront versus at discharge in AHF patients with CRS	Spironolactone use upfront in AHF patients at high risk for cardiorenal syndrome is safe and increases natriuresis.	N/A

(5) Du et al, 2021 (56)	RCT	40 with type I CRS	Conventional treatment grp (23) in the control group (15 males and 8 females, with mean age 77.16 ± 6.57 years) Nicorandin treatment grp 22 (15 males and 7 females,, with an average age of 75.48 ± 6.02 years)	LVEF Conventional treatment grp 22.26 ± 3.36 (increase to 36.04 ± 3.91) Nicorandin treatment grp 23.91 ± 2.24 (increase to 43.45 ± 3.29)	S Cr (μmoL/L) Conventional treatment grp 207.12 ± 43.96 (decrease to 187.62 ± 44.69*) Nicorandin treatment grp 220.61 ± 46.39 (decrease to 117.27 ± 13.41*†)	urine KIM-1, NGAL, and IL-18 levels of the 2 groups after treatment were lower than those before treatment	nicorandil treatment significantly decreased BNP, Scr, and Cys-C levels and increased LVEF		single center, small sample, and short-term study
(6) Buckley et al, 2022 (57)	RCT Post hoc analysis	22	median ages in the anakinra (n=15) and placebo (n=7) groups were 57 (55–69) and 64 (59–70) years		estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min/1.73 m2		anti-inflammatory effects of 2 weeks of anakinra 100 mg daily or placebo within the subgroup	At 2 weeks, anakinra had reduced CRP significantly by 84% (−92 to −2%) to 1.3 (0.7–2.2) mg/L (P=0.02) whereas placebo had no effect (−22% (−30 to 26%); P=0.94)	Lack of stratification according to CKD status at randomization and the small sample size, which may explain the lack of significant anti-inflammatory effects at 12-weeks
(7) Shao et al, 2018 (58)	RCT	36 patients with Refractory CHF (Type 2 CRS and Non type 2 CRS)	Type 2 CRS grp 53.6 ± 15.4 yrs Non Type 2 CRS grp 68.3 ± 12.7**	NYHA 3(42.9% of Type 2 CRS, 40.9 of non Type 2 CRS) NYHA 4(57.1% of Type 2 CRS, 59.1of non Type 2 CRS)	eGFR Type 2 CRS grp 27.8 ± 9.87 Non Type 2 CRS grp 15.1 ± 3.51**		effectiveness and safety of peritoneal dialysis (PD)	type 2 CRS was an independent risk factor for short survival time on PD. The benefit of PD on the improvement of survival and LVEF was limited to non CRS patients, but absent from CRS patients	
(8) Chunbo Chen at al 2016 (45)	RCT	213 pt with acute decompensated heart failure who developed kidney injury	66.8617.6 yrs of pts with AKI progression 70.6612.2 yrs without AKI progression	LVEF 42 (40–63) IN pts with AKI progression 41 (36–58) in without AKI progression	1.4560.7 in pts with AKI progression 1.3060.5without AKI progression	Whether renal injury biomarkers (6 = urinary angiotensinogen (uAGT), urinary neutrophil gelatinase-associated lipocalin (uNGAL), plasma neutrophil gelatinase-associated lipocalin, urinary IL-18 (uIL-18), urinary kidney injury molecule-1, and urinary albumin-to-creatinine ratio) measured at time of AKI diagnosis can predict worsening of AKI	None	uAGT was the best predictor for both primary and secondary outcomes	-The number of outcomes was relatively small -were not able to use urine output for AKI diagnosis because an indwelling urinary catheter was not present in most of the patients
(9) Vandenberghe et al 2015 (42)	Meta-analysis							-Increasing AKI severity was associated with worse outcomes. (AKI was associated with an increased mortality rate , a longer length of stay in the intensive care unit and a longer LOS in hospital) - RRT had an even greater impact compared to AKI	

(10) Johan Lassus Et al. 2007 (37)	Prospective, observational multicentric study	AHF patients eligible for hospitalisation n=620	74.8 years 50%-females	NYHA class 3 or 4 LVEF>45%	Creatinine levels	Cystatin C	Cystatin C, creatinine, age, gender, and systolic blood pressure on admission were identified as independent prognostic risk factors. in patients with normal plasma creatinine, elevated cystatin C was associated with significantly higher mortality at 12 months:	Categorizing patients in tertiles of cystatin C yielded three separate risk groups with low, medium, and high 1-year mortality Low-cystatin c,1.13mg/L Medium-cystatin c 1.13-1.55mg/L High-cystatin c>1.55mg/Ll	
11. Wilfried Mullens Et al, 2008 (38)	Cohort study	Patients admitted to specialzed heart failure ICU n=40	59+/-13 years	LVEF= 19+/-9%	Baseline creatinine= 2.0+/-0.9 mg/dl	Baseline intra abdominal pressure		Strong correlation was observed between reduction in IAP and improved renal function in patients with elevated baseline IAP	
(12) Wilfried Mullens Et al, 2008 33	COHORT STUDY	Patients with acute heart failure presented to university affiliated hospitals n=720		NT-pro BNP	GFR	NT-proBNP		A)GFR<60 ml,NT proBNP>4,467 - worse prognosis B) NTpro BNP below median is not influenced by renal impairment	
(13) John edward Et al, 2009 29	Case presentation	74 year female patient with heart failure	74 yrs old female	EF<20%		Neurohumoral mechanisms in heart failure	Pharmacological disruption of NH pathways early in HF may prevent CRS and may improve outcomes	Imbalance of NH effectors causes congestion leading to vicious cycle of congestion,renal dysfunction,and worsening of HF	Prognostic factors for activation of NH pathways is not mentioned
(14) Wenxue Hu at al 2016	Retrospective observational cohort study	312 adults	>60years old	Acute heart failure patients	GFR			Reduced basic eGFR, lower serum albumin and use of diuretics are risk factors for the occurrence of CRS1 in elderly patients, while use of diuretics, beta blockers and dialysis during hospitalization are predictors of in-hospital mortality in patients with CRS1	

(15) Palazzuoli et al, 2010	RCT		1)HB group A 12.3 ± 0.6; group B 11.7 ± 0.8; control group 10.6 ± 0.5 g/dl 2)HCT group A 34.2 ± 2.3, group B 34 ± 2, control group 32.3 ± 1.8% P < 0.01; 3)RBC, group A 3.9 ± 0.2, group B 3.8 ± 0.2, control group 3.3 ± 0.2,	BNP group A: 335 ± 138 vs. group B: 449 ± 274 pg/ml control group 582 ± 209 pg/ml		Effect of EPO on BNP levels and renal function in CRS syndrome		EPO treatment reduces BNP levels and hospitalization rate in patients with cardio-renal anemia syndrome. The correction of anemia by EPO treatment appears able to improve clinical outcome in this subset of patients with heart failure.	
(16) Tamhane et al, 2008 17	RCT	n=127 admitted in cardiac rehabilitation unit	HB	Creatinine clearance				Rehospitalization rates were increased two- and fivefold in lower compared to higher quintiles of hemoglobin and creatinine clearance, respectively. Anemia predicted rehospitalization in patients with renal dysfunction.	
(17) Virzi et al, 2019	observational study	31 AHF patients and 20 CRS type 1 (the cause of AKI was presumed to be related to cardiac dysfunction) and 17 healthy volunteers without AHF, AKI or CKD, as control group (CTR)					LPS levels resulted significantly higher in CRS type 1 patients compared with AHF	significant increase in LPS, TNF-α, IL-6, IL-18 and MPO levels in CRS type 1 and AHF group compared to Control grp.	
(18) Nelson et al, 2010 (20)	observational study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8673183/	n=10 The patients were required to be admitted to the hospital with an acute illness and to have acute kidney failure defined as per RIFLE criteria	Mean age : 62.6	BMI>30kg/m2 LVEF>50%			Association of obesity with worsening of renal function	Obese patients with preserved EF and acute illness, there was a trend of developing acute renal failure, right-sided volume overload, and pulmonary hypertension.	
(19) Palazzuoli at al 2014	Cross sectional study https://www.karger.com/Article/FullText/368375	n=246 Patients admitted in department of internal medicine, cardiology unit with diagnosis of acute decompensated heart failure	Mean age:		eGFR=50ml/min/1.73m2 S.creatinine=1.4mg/dl	TNF,NGAL,Tnt,osteoprotegrin		HF patients who displayed moderate kidney dysfunction had a significant increase in renal tubular (NGAL) and systemic biomarkers (BUN and TnT) compared to HF patients without RI.	First limitation is the small sample size of the population we studied; secondly, RI of the enrolled patients could have different pathophysiological mechanisms and timing (i.e. WRF, CKD, and AKI)

20 Tasic et al, 2016	Observational Study https://pubmed.ncbi.nlm.nih.gov/26989395/	N = 114 (79 patients divided into subgroups of acute and chronic cardiorenal syndromes and 35 volunteers)	Mean age Clinical Group 70.72 ± 9.26 Control Group = 69.55 ± 32	Ejection fraction, % Clinical Group 46.84 ± 14.08 Control Group = 72.80 ± 2.95	GFR Clinical Group 53.15 ± 23.61 Control Group = 92.32 ± 17.92	Cystatin C, glomerular filtration rate	N/A	Cystatin C, glomerular filtration rate measured by the MDRD equation and XOD were independent risk factors for acute cardiorenal syndrome, while age remained an independent risk factor for chronic cardiorenal syndrome.	N/A
21 Kremneva et al, 2018	Observational Study https://pubmed.ncbi.nlm.nih.gov/30701902/	90 patients (pts) undergoing CABG	Age 58±7 years	Chronic heart failure, functional class II (53.3% pts), functional class III (46.7% pts). Multi-vessel coronary lesions in 75.6% pts.	N/A	N/A	N/A	The development of AKI was associated with higher levels of troponin T after CABG	N/A

Limitations

In numerous investigations, renal function was assessed using serum Creatinine. Nevertheless, it is not the most accurate means of assessing renal function due to its fluctuation with age, sex, body mass, and physical activity. Urinary output by indwelling catheter is a superior method, but its use is restricted due to the fact that not all patients will be catheterized and the danger of urinary tract infection associated with unneeded catheterization. In addition, the bulk of the included research are monocentric. There is a need for additional multi centric studies since ethnicity and observer biases can influence the outcomes of single-center research. While some studies are constrained by their small sample size, others have a shorter follow-up period, making it difficult to assign long-term effects.

Discussion

CRS is defined as a pathophysiologic condition of the heart and kidneys in which acute or chronic malfunction of one organ can cause acute or chronic dysfunction of the other, and is categorized into five kinds [11].

Cardiorenal Syndrome: Classification, Epidemiology, and Risk Factors

Type 1 CRS: abrupt decline in cardiac function leading to acute renal damage (AKI). It occurs in a third of hospitalized patients with acute heart failure (HF) (Forman, Butler et al. 2004) and can be the result of chronic illness in one or both organs. AKI is characterized according to the KDIGO 2012 criteria (serum creatinine (SC) rise 0.3 mg/dL within 48 hours or 50 percent of starting value within seven days) [12]. The phrase "worsening renal function" (WRF) should also be familiar, typically defined as an increase in CS at hospital discharge of at least 0.3 mg/ dL or 25% with respect to the numbers at admission, as this parameter is employed in virtually all studies as a surrogate outcome measure of bad prognosis [13].

Acute deterioration of the heart state, such as ischemia insult or cardiac surgery complication, etc., is a risk factor for AKI [14]. Any disturbance in the hemodynamic mechanism, in the context of ADHF in CRS type 1, can decrease the GFR as a result of decreased renal artery flow. Non-Hemodynamic processes include the SNS, RAAS activation, chronic inflammation, and an imbalance in ROS/ NO production. Obesity-related glomerulopathy has been defined as a hyperfiltration disorder that leads to CKD and increases the risk of CRS in obese persons without diabetes.

Type 2 CRS: is a persistent heart failure that causes chronic kidney disease (CKD). It is detected in 42% of individuals and doubles the death rate [15]. The absence of a link between renal function and left ventricular ejection fraction (LVEF) shows that this relationship is more complex than a simple decrease in cardiac pump capacity [16].

Diuresis-associated hypovolemia, early administration of the RAAS blockade, and drug-induced hypotension have all been implicated in the onset or progression of CRS type 2 [17]. Due to the danger of hypokalemia, hypotension, significant neuro hormonal activation, and potential renal impairment, the use of high doses of IV loop diuretics in patients with CHF whose signs and symptoms are satisfactorily managed should be strongly avoided. Iatrogenic effects can frequently account for as much renal damage as congestive nephropathy itself [1, 18].

Type 3 CRS: AKI leading to acute cardiac injury, such as ischemia, arrhythmias, or acute HF. Multiple mechanisms are present [11, 19]. Uremic toxins lower contractile function and cause pericarditis; however, the precise causal agents have not been discovered [20]. Volume overload induces pulmonary edema, which is exacerbated by vasoconstriction of pulmonary arteries due to metabolic acidosis, which in turn promotes arrhythmias and hyperkalemia [11]. AKI is accompanied by an inflammatory response that impairs myocardial function [19]. AKI appears to affect over 70% of ICU patients, with 5-25% of patients developing severe AKI and 50-80% fatality rates [21].

High-risk individuals should avoid or minimize nephrotoxic drugs and procedures to prevent AKI, according to RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease) and AKIN (Acute Kidney Injury Network) guidelines. For instance, a combination of vancomycin and aminoglycoside, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, and diuretics.

Type 4 CRS: Chronic kidney disease that leads to heart disease by ventricular hypertrophy, diastolic dysfunction, and an increase in cardiovascular events (CVEs) [22]. As renal

function or albuminuria deteriorate, mortality and CVEs rise. In a meta-analysis of 1,024,977 patients, the hazard ratio (HR) for cardiovascular death was 1.24 for patients with a calculated glomerular filtration rate (cGFR) of 74 to 60 mL/min/1.73 m2 compared to 19.9 for patients with a cGFR 15 mL/min/1.73 m2 (Forman, Butler et al. 2004). Interestingly, hyper filtration (cGFR > 105 mL/min/1.73 m2) was also related with higher mortality when accompanied by an albumin/creatinine ratio of at least 10 mg/g in the urine [23].

CKD can indirectly (by increasing ischemic heart disease) and directly (by causing left ventricular hypertrophy due to pressure and volume overload) contribute to heart disease [24]. Left ventricular hypertrophy is particularly prevalent in hemodialysis patients and is responsible for later heart failure hospitalizations. In hemodialysis and predialysis patients, concomitant diseases such as hypertension and calcific valvular disease cause pressure overload leading to left ventricular hypertrophy {Van Sloten, 2012 #1}. As a result of the 'osteoblastic' transformation of vascular smooth muscle cells, hyperphosphatemia and secondary hyperparathyroidism (also known as CKD mineral and bone disease) can cause ossification of heart arteries and valves. Hypertension can also lead to the hardening of blood vessels that determines pressure overload. Arrhythmias, particularly atrial fibrillation and ventricular tachyarrhythmias, are more prevalent in CKD patients, especially those undergoing dialysis.

Type 5 CRS: concurrent renal and cardiac dysfunction related to an acute or chronic systemic illness, including sepsis, systemic lupus erythematosus, diabetes, hypertension, sarcoidosis, or amyloidosis, among others [22].

Risk factors include sepsis, infections, medications, poisons, and connective tissue illnesses such as lupus, granulomatosis with polyangiitis, and sarcoidosis. In contrast, CRS-5 has a more subtle onset in cirrhotic liver disease patients, and renal and heart dysfunction may progress gradually until a critical threshold is reached and full decompensation occurs.

Up to 40% of decompensated HF patients exhibit with CRS 1. The ADHERE trial indicated that just 9 percent of hospitalized patients with acute HF had normal renal function [2, 25]. 49 percent of patients with HF have been reported to have CKD [15]. In general, CKD is associated with a more than twofold increase in all-cause mortality in individuals with HF [15]. Patients with acute CRS had a threefold higher mortality risk than those with isolated HF or CKD, and those with type 4 CRS have a 49% higher mortality risk [26]. The impact of chronic kidney disease on medium- and long-term mortality is independent of the clinical phase as defined by the NYHA classification [27]. In HF, a 1 mg/dL increase in SC raises the risk of mortality by 7%, and a 10mL/min/1.73 m2 drop in GFRc increases the risk of death by 23%. [28, 25]. 16% and 20% of patients with CRS 2 and 4 had an acute form, respectively. In contrast, 5% and 10%, respectively, of individuals whose initial presentation was acute for types 1 and 3 developed the chronic form [28]. Most studies evaluating risk factors for CRS have focused on the occurrence of WRF in patients with CRS 1, with diabetes, hypertension, advanced age, and underlying CKD being the most prevalent.

The Pathophysiology of Disease

Mechanism of Disease Process

Multiple pathophysiologic processes are implicated in CRS, which contributes to some of the challenges in diagnosing, researching, and treating the disorder (hemodynamic, hormonal, and inflammatory). Consequently, despite the fact that it is simpler to study individual pathophysiologic processes, these processes must be viewed as part of a wider, diverse, and complex pathophysiology. In addition, the significance and influence of each phase vary based on the patient's clinical condition.

1. The Significance of Central Venous and Abdominal Pressure

Elevated intra-abdominal pressure (IAP) can lead to intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) in severe cases. These conditions are typically associated with surgical complications and can contribute to the pathophysiology of CRS.

ADHF is associated with volume overload and elevated central venous pressure (CVP). To maintain blood flow throughout the vascular system, the capillary network must have an acceptable pressure gradient. Elevated venous pressures diminish the gradient for forward blood flow through the renal vasculature, causing congestion, glomerular dysfunction, and a decrease in urine production.

2. Role of Cardiac Output and Cardiac Index

Initially, it was believed that a significant portion of the progressive deterioration in renal function observed in HF was due to poor renal perfusion resulting from a decreased cardiac output. Insufficient renal blood flow or perfusion pressure causes renin release by the juxtaglomerular cells of the afferent arterioles due to a low flow state in the ascending limb of the loop of Henle and pressure-sensing baroreceptors. This results in sodium retention, increased vascular congestion, and further deterioration of renal function due to constriction of renal afferent arteriolar vasculature.

3. Role of Neuro hormonal Dysregulation

Renin angiotensin aldosterone system (RAAS) plays a crucial role in the advancement of renal damage and the deterioration of heart failure. Adenosine and arginine play a part as well.

4. Role of Oxidative Stress

Oxidative stress is defined as an imbalance between oxidants and antioxidants that leads to an excessive buildup of oxidants and cellular damage {Sies, 1997 #2}.

ROS are produced as byproducts of cellular metabolism, predominantly in the mitochondria.

5. Role of Inflammatory Mediators

Pro-inflammatory cytokines include tumor necrosis factor-(TNF-) and TNF- related weak inducer of apoptosis (TWEAK), interleukin-1 (IL-1) family members, and interleukin-6 (IL-6) have been linked to both HF and CKD. CRP contributes to the development of atherosclerosis {Torzewski, 1998 #3} {Arici, 2001 #4} (74, 75).

6. Role of Renal Failure-Related Disturbances

Protein-bound uremic toxins (PBUT) have a patent connection with cardiovascular disease (CVD), whereas Indoxyl sulphate (IS) and p-crestyl sulphate (PCS) play a role in the advancement of CRS.

7. Role of Anemia

Anemia can contribute to the pathophysiology of CRS in multiple ways, such as by causing ischemia injury to the heart and kidneys due to a lack of oxygen. Because RBCs contain several antioxidants, anemia increases oxidative stress. Tissue ischemia and peripheral vasodilation resulting from anemia may

activate SNS, RAAS, and ADH, resulting in vasoconstriction, chronic venous congestion, and progressive nephron loss and interstitial fibrosis.

8. Pathogenesis of Type 5 Chronic Respiratory Syndrome

Type 5 CRS (CRS-5) arises when a severe systemic illness concurrently damages the heart and the kidneys. CRS-5 has been divided into four stages based on the etiology and severity of the disease process: hyperactive acute, acute, subacute, and chronic. Injuries to the kidney and heart are frequently mediated by pro-inflammatory cytokines, complement factors, and RAAS activation, which are frequently the final common pathway for different types of CRS.

Effect of Modifiable Risk Factors on Prognosis and Outcome

1. Obesity

Obesity increases blood volume, metabolic demands of tissues, and epicardia fat, which can enter the heart. This probably has long-term negative effects on the heart. Eventually, the establishment of a high-output cardiac state with increased LV stroke work leads to LV hypertrophy and increased ventricular wall stress. This results in diastolic dysfunction and compensatory eccentric LV hypertrophy [29]. Their elevated pulmonary pressures were likely attributable to the limited proportion of their group who had previously been diagnosed with OSA. Given the presence of lower extremity edema and pulmonary hypertension and the absence of other causes of pulmonary hypertension, such as idiopathic primary pulmonary hypertension, sarcoidosis, or connective tissue diseases, it was clinically reasonable to suspect that more patients had untreated sleep apnea [29]. The researchers discovered that glomerular hyperfiltration was significantly associated with metabolic risk clusters containing at least three risk variables. Acute renal functional impairments were particularly connected to obesity (increased leptin levels and anthropometric variables) and high blood pressure. The authors hypothesized, based on these findings, that glomerular hyperfiltration was predominantly caused by increased adiposity, notably the production of inflammatory adipokines by visceral fat [30]. The extent to which this hyperfiltration results in glomerular and tubulointerstitial fibrosis and progressive renal disease may rely on various factors including systemic and renal inflammation, reactive oxygen species, and others [30].

2. Glycemic Control

In their investigation, diabetes and uncontrolled hypertension were found as the two most important risk factors in patients with CRS. As demonstrated by the model developed by Kishimoto et al., it has been postulated that renal injury brought on by diabetes and/or hypertension and heart failure interacts with a connected and mutually reinforcing pathophysiology [8]. Hyperinsulinemia can reduce the quantity of uric acid excreted by the kidneys due to insulin's ability to stimulate the urate-anion exchanger and/or sodium-dependent anion co-transporter in the brush border membranes of the renal proximal tubule and enhance urea reabsorption [30].

3. Smoking

The authors noted that HTN, CAD, smoking, lower eGFR, low ejection fraction, and sepsis were risk factors for worse outcomes in all types of CRS [9].

4. Hypertension

According to the authors, hypertension is a major contributor to the development of CRS. Understanding the state of congestive heart failure requires that the kidneys operate properly. The implications of modest renal insufficiency on the prognosis of individuals with heart failure, particularly those with asymptomatic left ventricular dysfunction [31].

5. Effect of No modifiable Risk Factors on Outcome and Prognosis

Age-related Changes

Greater than 65-year-old individuals with CHF have an increase in systemic vascular resistance and a trend toward a decrease in heart rate with aging.

Serum levels of both urea nitrogen and creatinine increased with age. Detailed renal studies confirmed a decline in glomerular filtration rate and a no compensatory filtration fraction with increasing renal vascular resistance. Increased circulating norepinephrine is associated with increased vasoconstriction (or lower compliance) and impaired heart rate response in elderly individuals with CHF. In addition, the renal function of the elderly patient with CHF is severely impaired.

Effect of Renal and Cardiovascular Function Parameters

1.GFR, Creatinine in Serum, and Creatinine Clearance

The AKI is defined using KDIGO Clinical Practice Guidelines. Important for patient care is the ability to predict the clinical course, development, and outcome of renal disease. Serum creatinine levels at the time of AKI diagnosis have been reported to be considerably higher in patients who develop to AKI [33]. However, creatinine levels in AHF patients may be obscured by a variety of variables, including muscular atrophy, inadequate protein consumption, and fluid retention [33]. The study revealed that creatinine clearance is another key predictor of rehospitalization rates in CRS patients.

2. AKI and Biomarkers

• Classical Biomarkers

Cystatin C (CysC) is an endogenous inhibitor of cysteine proteinase that is reabsorbed and catalyzed by renal tubular cells. Serum creatinine (SCr), albuminuria, and cystatin C (CysC) are regarded as the standard indicators for evaluating kidney function in any type of renal pathology. Urine output and eGFR are also frequently employed. Risk of progression to CRS is associated with elevated xanthine oxidoreductase activity (XOA) and CysC values, and decreased GFR [32].

• Urine Biomarkers

Neutrophil gelatinase-associated lipocalin (NGAL) is one of the most frequently used indicators for evaluating renal function in CRS patients. It can be measured in both plasma and urine; however, the urinary test has been found to be more sensitive and specific in predicting patient outcomes [33]. It rapidly increases with the beginning of AKI. Its levels also associated with an increase in serum creatinine. Even though another Urinary Protein panel is now used for measuring cardiac outcomes, it could be effective for determining CRS outcomes. Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein located in the apical membrane of the proximal tubule. N-acetyl-D-glucosaminidase (NAG) is a lysosomal enzyme present in proximal tubular cells and filtered through glomerular filtration. Higher levels of the biomarkers urinary angiotensinogen, urinary enzyme N-acetyl-d-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin 18 (IL-18), and kidney injury molecule 1 (KIM-1) at the time of CRS diagnosis were also identified as predictors of AKI progression [33]. Metallopeptidase inhibitor TIMP 2 and insulin-like growth factor-binding protein

7 (IGFBP7) were discovered to be higher in patients with CRS than in people without CRS [34].

• Serum Biomarkers

At the time of CRS diagnosis, high sensitivity troponin I (hs-cTnI) has been demonstrated to be beneficial in risk categorization for unfavorable outcomes in CRS patients. 2-microglobulin (b2M) and tissue inhibitor of metalloproteinase 1 (TIMP 1) were also associated with cardiorenal impairment severity [35]. They also linked with increased proBNP levels, lower ejection fractions, and decreased GFR [36].

• Novel Biomarkers

In the past decade, tremendous progress has been made in our hunt for accessible biomarkers of kidney function that can guide treatment results [37]. Every 0.1 unit increase in relative wall thickness was associated with a 1.292-fold rise in serum hepcidin, as determined by Kim et al. in 2020 [38]. The soluble urokinase-type plasminogen activator receptor (suPAR) was identified by Nikorowitsch et al. in 2020 as a crucial biomarker for cardiovascular outcomes [39]. Placental growth factor (PlGF) is an additional valuable biomarker for predicting worse renal outcomes in CRS as well as in CKD patients alone. In acutely decompensated HF patients, elevated PIGF levels were observed to be related with increased all-cause and cardiovascular mortality [40]. The ratio of urine podocin to creatinine (UP/Cr) is a promising biomarker that is still under development. In a study of a population of dogs, its levels were evaluated by separating them into control, heart disease, and kidney disease groups. Significantly, greater amounts were reported in the heart disease and kidney disease groups compared to the control group [41]. Urinary cofilin-1, a de-differentiator modulator in renal tubular cells, is a valuable biomarker of both the severity of acute kidney injury and heart failure.

3. BNP, NT-Pro BNP and Natriuretic Peptides

The natriuretic peptides are a set of structurally related but genetically different peptides with various effects on cardiovascular, renal, and endocrine homeostasis.

BNP is derived from myocardial cells. It binds to the natriuretic peptide-A receptor and, through 3',5'-cyclic guanosine monophosphate (cGMP), promotes natriuresis, vasodilation, renin inhibition, antimitogenicity, and lusitropic characteristics Cardiac and renal dysfunction are intimately related on a neurohumoral basis via the renin-angiotensin-aldosterone system and its antagonists BNP,NT-pro BNP, in addition to sharing a high degree of similarity in terms of risk factors for their development. The combined use of cardiac, NT-pro BNP, and renal, GFR, measures enabled the identification of heart failure patients at a higher risk for short-term mortality Gardner et al. show that NT-pro BNP maintains a favorable prognosis for individuals with heart failure and renal impairment. Both BNP and NT-pro BNP clearance is partially dependent on renal function; hence, kidney failure may result in passive buildup of either marker.

4. Tropoproteins

Cardiac troponins are a well-established prognostic indicator for patients with Acute Coronary Syndrome. In the absence of Acute Coronary Syndrome, they have recently been revealed to have prognostic value in heart failure and chronic renal disease. Troponin T is more predictive of CKD outcomes than Troponin I. Additionally; a meta-analysis has shown that elevated troponins are related with increased all-cause mortality in individuals with renal illness. Increased troponins in CKD patients are indicative of continued myocardial injury, left ventricular dilatation, and reduced left ventricular systolic and diastolic function, but cannot definitively determine the patient's coronary artery disease status.

5. CAD

The majority of prior research (4-6) have examined CKD as a risk factor for CVD. According to the study and its authors (Junichi Ishigami in JASN, February 2020), each of these main cardiovascular disorders was separately and strongly related with the likelihood of ESRD, with heart failure having the strongest association. The link was higher between heart failure with retained ejection fraction and mortality than between heart failure with reduced ejection fraction.

6. LV Ejection Fraction

Low ejection fraction is related with a poor prognosis in all Cardiorenal syndromes, according to a study by Prothasis et al. in 2020. Similar association between Ejection fraction and rehospitalization was discovered by Salim et al. in their 2017 study. Additionally, CRS patients tended to have smaller ejection fractions than those without CRS.

Prognostic impact of definitive Treatments

1. Diuretics

Cardiorenal syndrome Type 1 is typically associated with Acute Decompensated Heart Failure (Ranco et al, 2010) As with ADHF, the primary emphasis of treatment for patients with CRS Type 1 is relieving venous congestion, and diuretics are recommended. However, the presence of concurrent renal impairment complicates the situation. In a matter of days, intravenous loop diuretics decrease renal function despite alleviating venous congestion. This has been identified as an independent risk factor for worse patient outcomes [17]. This is caused by a diuresis-induced stimulation of the RAAS, which results in sodium retention and precipitates CRS via renovascular processes. Also, not all patients exhibit an effective response to IV Furosemide, hence the inclusion of another diuretic - Thiazide or Spironolactone - has been suggested. Iiguez et al. determined that the diuretic effects of Combined Diuretic and Stepped Dose Furosemide were comparable. Another study evaluating the function of Spironolactone treatment upfront versus upon discharge in CRS patients with AHF revealed more natriuresis in the upfront group, but no difference in NT-proBNP levels. Numerous resistance mechanisms to diuretics have been examined. These include the suppression of diuretic secretion by other anions, such as NSAIDs, bile acids, and fatty acids, at the Organic Anion Transporters in the proximal tubules [42]. A kidney phenomenon involving counter regulatory sympathetic and neuro hormonal processes that counterbalance the diuretic impact is also responsible [43]. Nephron remodeling, which includes hypertrophy and hyperplasia of the distal convoluted tubule and collecting tubules, as well as an increase in salt reabsorption in these segments, may also play a role [44, 45]

2. Anti-inflammatory: Anti TNF, Anakinra

Cardiopulmonary bypass and renal ischemia-reperfusion injury initiate a sequence of events that leads in cellular damage and organ failure. In reaction to ischemia and reperfusion, both the kidney and the heart release Tumor Necrosis Factor (TNF), a potent proinflammatory cytokine. Cardiopulmonary bypass generates TNF, which results in glomerular fibrin deposition, cellular infiltration, and vasoconstriction, hence decreasing the glomerular filtration rate (GFR). The signaling route that renal ischemia-reperfusion uses to stimulate TNF production is beginning to become evident [46]. Therefore, anti-TNF medication can minimize these consequences.

3. Peritoneal Dialysis

According to the authors, the potential for high rates of technique failure and PD-related side effects, such as peritonitis and catheter malfunction, is one of the primary concerns with the use of PD in cardiorenal. However, because to recent breakthroughs in PD, the approach for surviving PD is now generally accepted. They demonstrated that PD therapy is only palliative and did not increase long-term survival for RCHF patients with type 2 CRS. Our findings revealed that PD is a safe and feasible therapeutic alternative for individuals with type 2 CRS whose major treatment objective is symptom reduction as opposed to long-term survival [47].

Conclusion

Kidney disease and cardiovascular disease are more prevalent and frequently overlap. In this systematic review, we seek to determine the significance of knowing the risk factors associated with the development of cardiorenal syndrome and how these factors lead to a poor prognosis. The cardiorenal syndrome is quite prevalent in patients with heart failure. Cardiorenal syndrome is more likely to develop in patients who have had at least two prior hospitalizations, sepsis, and a history of CAD. More than 60 years of age, smoking, hypertension, CAD, diabetes, sepsis, and laboratory parameters such as blood urea, serum creatinine, eGFR, and LVEF were observed to be linked with death. CRS is related with advancing age, hypertension, diabetes, cardiovascular and kidney illnesses, high levels of BUN, creatinine, potassium, and albumin, all of which contribute to poor patient outcomes. More research is required to comprehend its pathogenesis and find viable treatment methods. Early identification and treatment of CRS are essential for preventing later problems and achieving a better prognosis and patient success. There is an urgent need for new research in this area to improve clinical outcomes.

References

1. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, et al. (2004) Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. Journal of the American College of Cardiology 43: 61-67.
2. Heywood JT (2005) The cardiorenal syndrome: lessons from the ADHERE database and treatment options. Heart failure reviews 9: 195-201.
3. House AA, Anand I, Bellomo R, Cruz D, Bobek I, et al. (2010) Definition and classification of Cardio-Renal Syndromes: workgroup statements from the 7th ADQI Consensus Conference. Nephrology Dialysis Transplantation 25: 1416-1420.
4. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, et al. (2016) Global prevalence of chronic kidney disease–a systematic review and meta-analysis. PloS one 11: e0158765.
5. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO (2013) Rehospitalization for heart failure: problems and perspectives. Journal of the American College of Cardiology 61: 391-403.
6. Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, et al. (2015) Cause of death in patients with reduced kidney function. Journal of the American Society of Nephrology 26: 2504-2511.
7. Kumar U, Wettersten N, Garimella PS (2019) Cardiorenal syndrome: pathophysiology. Cardiology clinics 37: 251-265.
8. Arous Salim ME (2017) Cardiorenal Syndrome Type 2: A Strong Prognostic Factor of Survival. International Journal of Cardiovascular Sciences.
9. Prothasis M, Varma A, Gaidhane S, Kumar S, Khatib N, et al. (2020) Prevalence, types, risk factors, and outcomes of cardiorenal syndrome in a rural population of central India: A cross-sectional study. Journal of Family Medicine and Primary Care 9: 4127.
10. Chen C, Yang X, Lei Y, Zha Y, Liu H, et al. (2016) Urinary Biomarkers at the Time of AKI Diagnosis as Predictors of Progression of AKI among Patients with Acute Cardiorenal Syndrome. Clinical journal of the American Society of Nephrology CJASN 11: 1536-1544.
11. Ronco C, McCullough PA, Anker SD (2010) Acute Dialysis Quality Initiative (ADQI) Consensus Group Cardiorenal syndromes: an executive summary from the Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Contrib Nephrol 165: 54-67.
12. Workgroup K (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2: 1-138.
13. Gudsoorkar PS, Thakar CV (2019) Acute kidney injury, heart failure, and health outcomes. Cardiology Clinics 37: 297-305.
14. Bagshaw SM, Cruz DN, Aspromonte N, Daliento L, Ronco F, et al. (2010) Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. Nephrology Dialysis Transplantation 25: 1406-1416.
15. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ et al. (2014) Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. European heart journal 35: 455-469.
16. Vickers NJ (2017) Animal communication: when i'm calling you, will you answer too? Current biology 27: R713-R715.
17. Liang KV, Williams AW, Greene EL, Redfield MM (2008) Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med 36: S75-S88.
18. Costanzo MR (2008) Ultrafiltration in the management of heart failure. Current Opinion in Critical Care 14: 524-530.
19. Shamseddin MK, Parfrey PS (2009) Mechanisms of the cardiorenal syndromes. Nature Reviews Nephrology 5: 641-649.
20. Meyer TW, Hostetter TH (2007) Uremia. New England Journal of Medicine 357: 1316-1325.
21. Dar O, Cowie MR (2008) Acute heart failure in the intensive care unit: epidemiology. Critical Care Medicine 36: S3-S8.
22. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, et al. (2010) Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. European heart journal 31: 703-711.
23. Fox C, Matsushita SK, Woodward M, Bilo HJ, Chalmers J, et al. (2012) Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. The Lancet 380: 1662-1673.
24. Di Lullo L, House A, Gorini A, Santoboni A, Russo D, et al. (2015) Chronic kidney disease and cardiovascular complications. Heart failure reviews 20: 259-272.
25. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, et al. (2007) High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. Journal of cardiac failure 13: 422-430.
26. Mavrakanas TA, Khattak A, Singh K, Charytan DM (2017) Epidemiology and natural history of the cardiorenal syndromes in a cohort with echocardiography. Clinical Journal of the American Society of Nephrology 12: 1624-1633.
27. Löfman I, Szummer K, Hagerman I, Dahlström U, Lund LH, et al. (2016) Prevalence and prognostic impact of kidney

disease on heart failure patients. Open heart 3: e000324.
28. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, et al. (2006) Renal impairment and outcomes in heart failure: systematic review and meta-analysis. Journal of the American College of Cardiology 47: 1987-1996.
29. Nelson R (2010) Obesity related Cardiorenal Syndrome. The JCH.
30. James R, Sowers AWC (2011) The Role of Overweight and Obesity in the Cardiorenal Syndrome. PMC.
31. Daniel L, Dries Exner DV, Domanski MJ, Greenberg B, Stevenson LW (2000) The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 35: 681-689.
32. Tasić D, Radenkovic S, Stojanovic D, Milojkovic M, Stojanovic M, et al. (2016) Crosstalk of Various Biomarkers That Might Provide Prompt Identification of Acute or Chronic Cardiorenal Syndromes. Cardiorenal medicine 6: 99-107.
33. Wagener G, Minhaz M, Mattis FA, Kim M, Emond JC, et al. (2011) Urinary neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after orthotopic liver transplantation. Nephrology, dialysis, transplantation. Official publication of the European Dialysis and Transplant Association - European Renal Association 26: 1717-1723.
34. Gunnerson KJ, Shaw AD, Chawla LS, Bihorac A, Al-Khafaji A, et al. (2016) TIMP2•IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients. The journal of trauma and acute care surgery 80: 243-249.
35. Atici A, Emet S, Cakmak R, Yuruyen G, Alibeyoglu A, et al. (2018) Type I cardiorenal syndrome in patients with acutely decompensated heart failure: the importance of new renal biomarkers. European review for medical and pharmacological sciences 22: 3534-3543.
36. Vianello A, Caponi L, Galetta F, Franzoni F, Taddei M, et al. (2015) β2-Microglobulin and TIMP1 Are Linked Together in Cardiorenal Remodeling and Failure. Cardiorenal medicine 5: 1-11.
37. Gembillo G, Visconti L, Giusti M, Siligato R, Gallo A, et al. (2021) Cardiorenal Syndrome: New Pathways and Novel Biomarkers. Biomolecules 11: 1581.
38. Kim GH (2020) Hepcidin as a Biomarker of Cardiorenal Syndrome. Journal of Korean medical science 35: e20.
39. Nikorowitsch J, Borchardt T, Appelbaum S, Ojeda F, Lackner KJ, et al. (2020) Cardio-Renal Biomarker Soluble Urokinase-Type Plasminogen Activator Receptor Is Associated With Cardiovascular Death and Myocardial Infarction in Patients With Coronary Artery Disease Independent of Troponin, C-Reactive Protein, and Renal Function. Journal of the American Heart Association 9: e015452.
40. Yasuki Nakada, Rika Kawakami, Masaru Matsui, Tomoya Ueda, Tomoya Nakano, et al. (2019) Decompensated Heart Failure. Circulation journal: official journal of the Japanese Circulation Society 83: 395-400.
41. Szczepankiewicz B, Paslawska U, Paslawski R, Gebarowski T, Zasada W, et al. (2019) The urine podocin/creatinine ratio as a novel biomarker of cardiorenal syndrome in dogs due to degenerative mitral valve disease. Journal of physiology and pharmacology: an official journal of the Polish Physiological Society 70: 229-238.
42. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, et al. (1995) Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. Clin Pharmacol Ther 57: 601-609.
43. Ellison DH (1991) The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med 114: 886-894.
44. Kaissling B, Bachmann S, Kriz W (1985) Structural adaptation of the distal convoluted tubule to prolonged furosemide treatment. Am J Physiol 248: F374-F381.
45. Ellison DH, Velazquez H, Wright FS (1989) Adaptation of the distal convoluted tubule of the rat. Structural and functional effects of dietary salt intake and chronic diuretic infusion. J Clin Invest 83: 113-126.
46. Meldrum DR, Donnahoo KK (1999) Role of TNF in Mediating Renal Insufficiency Following Cardiac Surgery: Evidence of a Postbypass Cardiorenal Syndrome. Journal of Surgical Research Home 85: 185-199.
47. Shao Q, Xia Y, Zhao M, Liu J, Zhang Q et al. (2018) Effectiveness and Safety of Peritoneal Dialysis Treatment in Patients with Refractory Congestive Heart Failure due to Chronic Cardiorenal Syndrome 2018: 6529283.